Preparation of 2-deoxy-2-*C*-*p*-tolylsulfonyl-β-D-glucopyranosyl *p*-tolyl sulfones having non-chair conformation and their elimination reactions†

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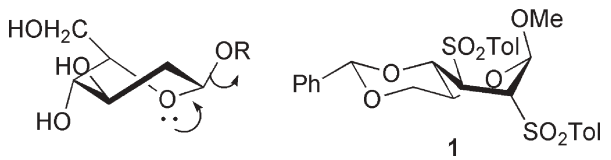
When the title sulfones, which have non-chair conformations, were stirred with silica gel, elimination of sulfinic acid occurred to give a 1-enitol derivative, if the hydroxyl group at C-6 was protected, whereas such an elimination did not proceed if the hydroxy group was free.

Replacement reactions at an anomeric center (C-1) are important in biological and chemical processes and hence they have been investigated extensively.[1] The theory of stereoelectronic effects predicts that in a β-D-glucopyranoside departure of a leaving group from C-1 should proceed through a non-chair conformation such as a boat or sofa form in which a lone pair on the ring oxygen atom can be antiperiplanar to the leaving group.[2] However, direct experimental evidence seems not to be presented, because a β-D-glucopyranoside inevitably occupies a chair conformation in solution. In fact, to our best knowledge, there is no report that describes a β-D-glucopyranosyl derivative which has a leaving group at C-1 taking up a non-chair conformation in solution.[3]



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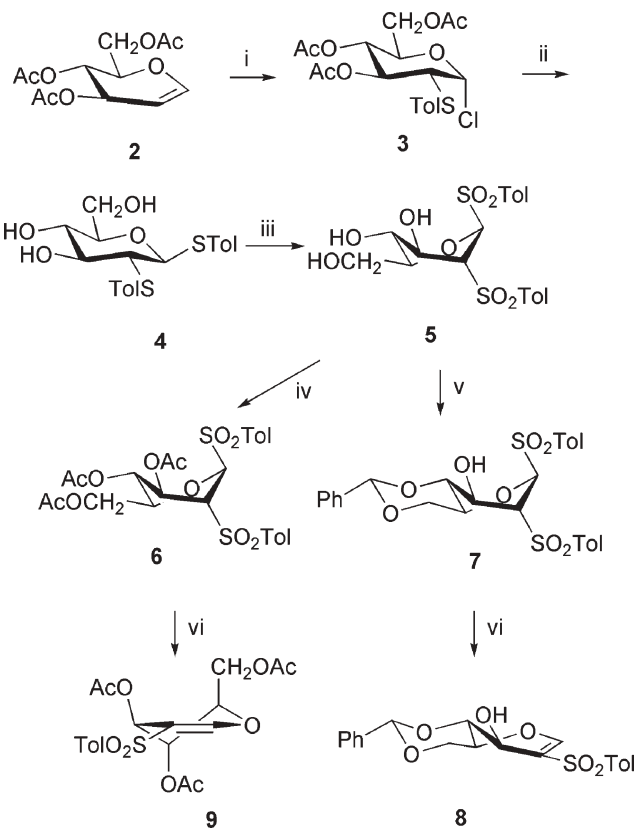
A sulfonyl group at C-1 behaves as a leaving group;[4] therefore, we have synthesized 2-*C*-*p*-tolylsulfonyl-β-D-glucopyranosyl *p*-tolyl sulfone, expecting that such a compound exceptionally occupies a non-chair conformation, because we found that methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-*C*-di-*p*-tolylsulfonyl-β-D-glucopyranoside (**1**) adopts a non-chair conformation in solution.[5]

The intended ditosyl derivative **5** was prepared by addition of *p*-tolylsulfenyl chloride to tri-*O*-acetyl-D-glucal (**2**),[6] followed by addition of sodium *p*-tolylthiolate in methanol, and then oxidation with *m*-chloroperbenzoic acid (Scheme 1). Compound **5**, as expected, occupies a non-chair conformation as judged from the coupling constants, $J_{1,2}$ 3.3, $J_{2,3}$ 5.4, $J_{3,4}$ 8.6, and $J_{4,5}$ 10.3 Hz. It is noteworthy that compound **5** occupies the non-chair conformation instead of a $^1C_4$ conformation. The latter conformation is observed, for example, in phenyl 1-seleno-2,3,4,6-tetrakis-*O*-triisopropylsilyl-β-D-glucopyranoside.[7] A non-chair conformation for **5** should be caused by steric hindrance due to the two vicinal equatorial tosyl groups[8] and a by strong bias for the hydroxymethyl group at C-5 to occupy the equatorial position.[9] Acetylation of **5** with acetic anhydride in the presence of catalytic amounts of boron trifluoride etherate gave the tri-*O*-acetate **6**.[10] Conventional benzylidenation of **5** gave the 4,6-*O*-benzylidene derivative **7** (Scheme 1). These derivatives again occupy a non-chair conformation. During column chromatography on silica gel (Merck silica gel 60, mesh), elimination of sulfinic acid partially occurred from the benzylidene derivative **7** to afford the 1-enitol derivative **8**, the structure of which was determined from ^{1}H NMR (δ, 7.87, d, $J_{1,3}$ 0.7 Hz, H-1), ^{13}C NMR (δ, 155.28, C-1; 119.53, C-2) and elemental analyses. When a neutral silica gel (Kanto, silica gel 60N, 40–50 μm) was



Scheme 1 *Reagents and conditions*: (i) TolSCl, CH_2Cl_2, room temp., 59 h, 63%; (ii) NaSTol, MeOH, Ar atmosphere, room temp., 8 h, 72%; (iii) *m*CPBA, CH_2Cl_2, Ar atmosphere, 1 h, 63%; (iv) Ac_2O, BF_3OEt_2, room temp., 20 h, 97%; (v) $PhCH(OMe)_2$, CSA, MeCN, room temp., 1 h, 91%; (vi) silica gel 60N, DMF, room temp., 24 h, 70% from **7** and 82% from **6**.

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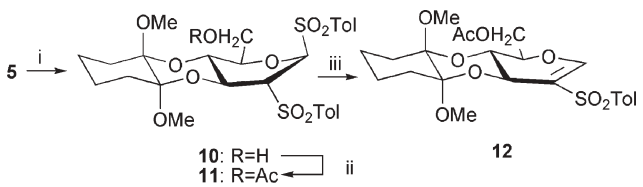
used, the decomposition was suppressed to give the benzylidene derivative **7** in 91% yield. When acetate **6** or benzylidene derivative **7** in DMF was stirred with silica gel (Merck) at room temperature for 24 h, elimination of sulfinic acid completely occurred to give the 1-enitols **9** and **8**, respectively, in high yields (Scheme 1). Similar treatment of the nonprotected **5**, however, resulted in the recovery of **5**. Thus, elimination of sulfinic acid was affected by the hydroxyl group at C-6; that is, if the hydroxyl group was free, the elimination reaction was suppressed, whereas it occurred smoothly, if the hydroxyl group was protected. Different from the 4,6-*O*-benzylidene derivative **8**, tri-*O*-acetyl-1-enitol **9** occupies a $^{5}H_{4}$ conformation, as judged from small coupling constants: $J_{3,4}$ 3.2 and $J_{4,5}$ 2.3 Hz. This is in good agreement with the case of 3,4,6-tri-*O*-acetyl-2-deoxy-2-nitro-D-glucal.[11]

To confirm the generality of the phenomenon, we have synthesized the cyclohexane-1,2-diacetal **10** and its 6-*O*-acetate **11** (Scheme 2).[12] These compounds again did not take up the $^{4}C_{1}$ conformation, but a $^{4}S_{O}$ or $_{4,O}B$-like conformation: $J_{1,2}$ 4.5, $J_{2,3}$ 9.7, $J_{3,4}$ 10.7, $J_{4,5}$ 10.5 Hz for **10** and $J_{1,2}$ 3.7, $J_{2,3}$ 9.2, $J_{3,4}$ 11.0, $J_{4,5}$ 10.3 Hz for **11**. The same treatment of the acetate **11** with silica gel (Merck), as described above, gave the 1-enitol **12** in 80% yield (Scheme 2), whereas even after 48 h the starting material was recovered in the case of the 6-O free **10**.



Scheme 2 *Reagents and conditions*: (i) 1,1,2,2-tetramethoxycyclohexane, $CH(OMe)_3$, CSA, MeOH, reflux for 18 h, 46%; (ii) Ac_2O, BF_3OEt_2, room temp., 99%; (iii) silica gel 60N in DMF, room temp., 24 h, 80%.

Although experimental evidence is not obtained at the present stage, hydrogen bonding between the hydroxyl group at C-6 and the ring oxygen atom (O-5) probably suppressed the elimination of the anomeric sulfonyl group.

Ab initio calculations (B3LYP/6-31+G*)[13] of model **13** (Fig. 1) for the benzylidene derivative **7** were in good agreement with experimental results; the non-chair conformer (C-3 and C-4 are slightly lower and upper, respectively, from the ideal $B_{2,5}$ conformation) was more stable than the $^{4}C_{1}$ conformer by 2.0 kcal mol^{-1}. STO-3G level calculations of model compound **14** (Fig. 1) for the cyclohexane-1,2-diacetal **10** indicated that a non-chair conformer (the pyranose ring occupies a $B_{O,3}$-like conformation, but its C-4 and C-5 take up fairly upper and slightly lower positions, respectively) is more stable than a chair conformer by 2.3 kcal mol^{-1}. During optimization at the 6-31G* level calculation, however, the chair and non-chair conformers gave the same non-chair conformer, which is in good agreement with the coupling constants observed.

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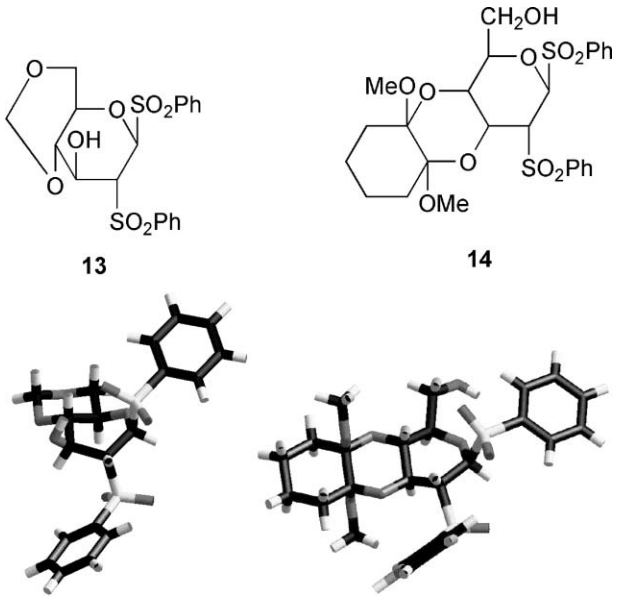

Fig. 1 Fully optimized structures of **13** (left) and **14** (right).

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10 **4**, $J_{1,2}$ 10.5, $J_{2,3}$ 10.2, $J_{3,4}$ 8.7, $J_{4,5}$ 9.4; **6**, $J_{1,2}$ 2.7, $J_{2,3}$ 2.9, $J_{3,4}$ 6.2, $J_{4,5}$ 9.7; **7**, $J_{1,2}$ 1.6, $J_{2,3}$ 2.9, $J_{3,4}$ 8.3, $J_{4,5}$ 10.2, $J_{5,6a}$ 10.2, $J_{5,6e}$ 5.3; **8**, $J_{1,3}$ 0.7, $J_{3,4}$ 7.3, $J_{4,5}$ 10.3, $J_{5,6a}$ 10.3, $J_{5,6e}$ 5.1; **12**, $J_{1,3}$ 1.4, $J_{3,4}$ 9.2, $J_{4,5}$ 10.8 Hz. In general, correlation between H-1 and H-5 is stronger than that of H-1 and H-3 or H-3 and H-5 because the distance between H-1 and H-5 is shorter than that of H-1 and H-3 or H-3 and H-5. In NOESY spectra, weak correlation between H-1 and H-5 was often observed in these non-chair conformers, suggesting that a small amount of $^{1}C_{4}$ conformer was also present in an equilibrium.

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